Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 2009;360:xxxx-xx.

Web Supplemental Appendix for NEAD 3 Year Old IQ Study: 4 tables & 5 figures

Web Table 1. Age 3 IQ Regression Model Results for the Primary Analysis of the Intent-To-Treat Group (n=309).[A]

	Coefficient [B] (95% CIs) and p-value for variable alone, unadjusted	**p-value for Variable in Model [C]**
Significant Variables in Primary Model		
AED Group (4 levels, p-value only) [D]	.007	.02
Maternal IQ [D]	0.4 (0.3, 0.5); p<.001	p<.001
Maternal Age [D]	1.0 (0.6, 1.3); p<.001	p<.001
Standardized Dose [D,E]	-0.1 (-0.2, 0.0); p=.13	p=.02
Gestational Age [D]	1.3 (0.3, 2.2); p=.008	p=.01
Preconception Folate Use [D]	9.1 (4.9, 13.4); p<.001	p=.02
Non-significant Variables When Added to Primary Model		

	Coefficient [B] **(95% CIs) and p-value for variable alone, unadjusted**	**p-value for Variable in Model** [C]
Epilepsy Etiology [F] (3 levels, p-value only)	.36	.77
Epilepsy Type: Localization Related	0.4 (-4.1, 4.8); p=.87	.71
Epilepsy Type: Idiopathic Generalized	-2.1 (-6.8, 2.5); p=.37	.51
Epilepsy Type: Generalized Tonic Clonic Seizures [G]	5.2 (-2.9, 13.4); p=.20	.65
No Convulsions During Pregnancy (3 levels, p-value only) [H]	.02	.72
> 5 Convulsions During Pregnancy (3 levels, p-value only) [H]	.03	.27
Education [I]	9.9 (5.2, 14.6); p<.001	.56
Employment	6.1 (1.6, 10.6); p=.008	.31
Race (4 levels, p-value only) [J]	.002	.22
Socioeconomic Status [K]	2.6 (1.8, 3.5); p<.001	.26
USA vs. UK Site	-0.2 (-4.7, 4.4); p=.94	.89

	Coefficient [B] (95% CIs) and p-value for variable alone, unadjusted	**p-value for Variable in Model [C]**
Alcohol Use	2.6 (-5.5, 10.8); p=.53	.63
Tobacco Use	-5.6 (-12.3, 1.1); p=.10	.80
Birth Weight	4.7 (1.4, 8.0); p=.005	.49
Wanted vs. Unwanted Pregnancy	10.3 (4.2, 16.3); p<.001	.61
Breastfed (3 levels, p-value only) [H]	.004	.55
Prior Pregnancy Complications	-0.0 (-4.6, 4.5); p=.99	.98
Prior Pregnancy Birth Defects	-2.6 (-10.5, 5.4); p=.53	.55
Complications During Current Pregnancy	-1.0 (-5.3, 3.4); p=.67	.88
Compliance (missed AED doses) (3 levels, p-value only) [H]	.10	.50

[A] Age 3 IQ imputed for 77 children without age 3 assessments from the original 309 live births (1 died from severe heart malformation, 6 enrolled from the UK study after 3 years/old, 31 withdrew prior to age 3, and 39 did not present for testing). [B] Estimated regression coefficient (non-ordered categorical variables have only p value), 95% CI = 95% Confidence Intervals; [C] Model includes AED, maternal IQ, maternal age,

standardized AED dose, gestational age, and preconception folate; [D] Variables in primary model; [E] Standardized dose for pregnancy average (see Methods); [F] Three epilepsy types: localization related, idiopathic generalized, & generalized tonic clonic unknown if partial or generalized; [G] Unknown if idiopathic generalized or secondary generalized localization related; [H] Three categories (yes, no, not reported); [I] Education ≤ or > high school; [J] Four categories: Caucasian, Black, Hispanic, other; [K] Hollingshead Index.[10]

Web Table 2. Age 3 IQ Regression Model Results for Age 2 & 3 Completers Sample (n=258).[A]

VARIABLE	**Coefficient[B] (95% CIs) and p-value for variable alone, unadjusted**	**P-value for Variable in Model[C]**
Significant Variables in Primary Model		
AED Group (4 levels, p-value only)[D]	.003	.02
Maternal IQ[D]	0.4 (0.3, 0.5); p<.001	<.001
Maternal Age[D]	1.0 (0.6, 1.3); p<.001	.002
Standardized Dose[D, E]	-0.1 (-0.2, 0.0); p=.17	.02
Gestational Age at Birth[D]	1.2 (0.3, 2.2); p=.01	.01
Preconception Folate Use[D]	9.2 (4.8, 13.7); p<.001	.02
Non-significant Variables When Added to Primary Model		
Epilepsy Type[F] (3 levels, p-value only)	p=.44	.67
Epilepsy Type: Localization Related	0.5 (-4.2, 5.1); p=.84	.73

VARIABLE	Coefficient [B] (95% CIs) and p-value for variable alone, unadjusted	P-value for Variable in Model [C]
Epilepsy Type: Idiopathic Generalized	-2.1 (-6.9, 2.8); p=0.40	.44
Epilepsy Type: Generalized Tonic Clonic Seizures [G]	4.8 (-3.6, 13.2); p=.26	.52
No Convulsions During Pregnancy (3 levels, p-value only) [H]	.02	.62
> 5 Convulsions During Pregnancy (3 levels, p-value only) [H]	.03	.19
Education [I]	10.8 (6.0, 15.7); p<.001	.45
Employment	6.2 (1.6, 10.8); p=.008	.30
Race (4 levels, p-value only) [J]	<.001	.08
Socioeconomic Status [K]	2.8 (1.9, 3.7); p<.001	.26
USA vs. UK Site	-1.0 (-5.9, 3.9); p=.70	.98

VARIABLE	Coefficient [B] (95% CIs) and p-value for variable alone, unadjusted	P-value for Variable in Model [C]
Alcohol Use	3.9 (-4.7, 12.4); p=.38	.51
Tobacco Use	-6.6 (-13.7, 0.5); p=.07	.69
Birth Weight	4.7 (1.4, 8.0); p=.006	.44
Wanted vs. Unwanted Pregnancy	10.4 (4.0, 16.8); p=.001	.60
Breastfed (3 levels, p-value only) [H]	.003	.50
Prior Pregnancy Complications	-0.0 (-4.8, 4.7); p=.99	.91
Prior Pregnancy Birth Defects	-3.4 (-11.6, 4.8); p=.42	.48
Complications During Current Pregnancy	-1.0 (-5.6, 3.6); p=.67	.94
Compliance (missed AED doses) (3 levels, p-value only) [H]	.12	.37

[A] Age 3 IQ imputed for 26 children with 2 year assessments only; [B] Estimated regression coefficient (non-ordered categorical variables have only p value), 95% CI = 95% Confidence Intervals; [C] Model includes AED, maternal IQ, maternal age, standardized AED dose, gestational age, and preconception folate; [D] Variables in primary model; [E] Standardized dose for pregnancy average (see Methods); [F] Three epilepsy types: localization related, idiopathic generalized, generalized tonic clonic unknown if partial or generalized; [G] Unknown if idiopathic generalized or secondary generalized localization related; [H] Three categories (yes, no, not reported); [I] Education $\underline{\leq}$ or > high school; [J] Four categories: Caucasian, Black, Hispanic, other; [K] Hollingshead Index[10]

Web Table 3. Age 3 IQ Regression Model Results for Age 3 Completers Sample (n=232).[A]

VARIABLE	Coefficient[B] (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model[C]
Significant Variables in Primary Model		
AED Group (4 levels, p-value only)[D]	.002	.01
Maternal IQ[D]	0.4 (0.3, 0.5); p<.001	<.001
Maternal Age[D]	1.1 (0.7, 1.4); p<.001	<.001
Standardized Dose[D, E]	-0.1 (-0.2, 0.0); p=.23	.03
Gestational Age at Birth[D]	1.3 (0.3, 2.3); p=.01	.02
Preconception Folate Use[D]	9.1 (4.6, 13.6); p<.001	.02
Non-significant Variables When Added to Primary Model		
Epilepsy Etiology[F] (3 levels, p-value only)	.21	.33
Epilepsy Type: Localization Related	2.1 (-2.6, 6.8); p=.37	.32

VARIABLE	Coefficient [B] (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model [C]
Epilepsy Type: Idiopathic Generalized	-3.9 (-8.8, 1.0); p=.11	.14
Epilepsy Type: Generalized Tonic Clonic Seizures [G]	4.7 (-3.7, 13.1); p=.27	.55
No Convulsions During Pregnancy (3 levels, p-value only) [H]	.02	.91
> 5 Convulsions During Pregnancy (3 levels, p-value only) [H]	.03	.26
Education [I]	11.4 (6.5, 16.3); p<.001	.36
Employment	7.2 (2.5, 11.9); p=.003	.26
Race (4 levels, p-value only) [J]	<.001	.06
Socioeconomic Status [K]	2.8 [(1.9, 3.7); p<.001	.30
USA vs. UK Site	-1.2 (-6.1, 3.7); p=.64	.98
Alcohol Use	3.2 (-5.5, 11.8); p=.47	.79
Tobacco Use	-7.6 (-14.7, -0.5); p=.04	.62

VARIABLE	Coefficient [B] (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model [C]
Birth Weight	4.1 (0.6, 7.5); p=.02	.84
Wanted vs. Unwanted Pregnancy	10.1 (3.7, 16.5); p=.002	.80
Breastfed (3 levels, p-value only) [H]	.005	.66
Prior Pregnancy Complications	1.0 (-3.8, 5.9); p=.67	.93
Prior Pregnancy Birth Defects	-3.0 (-11.4, 5.4); p=.48	.49
Complications During Current Pregnancy	0.3 (-4.4, 4.9); p=.91	.62
Compliance (missed AED doses) (3 levels, p-value only) [H]	.13	.42

[A] Only the 232 children with IQ assessment at age 3 included in this analysis.

[B] Estimated regression coefficient (non-ordered categorical variables have only p value), 95% CI = 95% Confidence Intervals; [C] Model includes AED, maternal IQ, maternal age, standardized AED dose, gestational age, and preconception folate; [D] Variable included in primary model; [E] Standardized dose for pregnancy average (see Methods); [F] Three epilepsy types: localization related, idiopathic generalized, &

generalized tonic clonic unknown if partial or generalized; [G] Unknown if idiopathic generalized or secondary generalized localization related; [H] Three categories (yes, no, not reported); [I] Education ≤ or > high school; [J] Four categories: Caucasian, Black, Hispanic, other; [K] Hollingshead Index.[10]

Web Table 4. Regression Model Results for Age 2 Sample (n=187).[A]

VARIABLE	Coefficient [B] (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model [C]
Variables in Primary Model		
AED Group (4 levels, p-value only)[D]	.03	.08 [A]
Maternal IQ [D]	0.4 (0.2, 0.5); p<.001	**<.001**
Maternal Age [D]	0.9 (0.4, 1.4); p<.001	**.04**
Standardized Dose [D, E]	-0.1 (-0.3, -0.0); p=.03	**.006**
Gestational Age at Birth [D]	1.0 (-0.1, 2.1); p=.07	.05
Preconception Folate Use [D]	9.8 (4.7, 14.9); p<.001	**.04**
Other Variables		
Epilepsy Etiology [F] (3 levels, p-value only)	.006	**.03** [A]
Epilepsy Type: Localization Related	-3.7 (-9.1, 1.6); p=.17	.57
Epilepsy Type: Idiopathic Generalized	-0.9 (-6.6, 4.8); p=.76	.29

VARIABLE	Coefficient [B] (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model [C]
Epilepsy Type: Generalized Tonic Clonic Tonic Seizures [G]	16.4 (6.4, 26.4); p=.002	**.008** [A]
No Convulsions During Pregnancy (3 levels, p-value only) [H]	.18	.49
> 5 Convulsions During Pregnancy (3 levels, p-value only) [H]	.48	.56
Education [I]	12.0 (6.4, 17.5); p<.001	.37
Employment	0.9 (-4.6, 6.4); p=.74	.48
Race (4 levels, p-value only) [J]	.02	.89
Socioeconomic Status [K]	2.6 (1.5, 3.6); p<.001	.79
USA vs. UK Site	-1.1 (-10.5, 8.2); p=.81	.60
Alcohol Use	-0.6 (-12.9, 11.6); p=.92	.92
Tobacco Use	-8.8 (-18.7, 1.0); p=.08	.96
Birth Weight	5.4 (1.6, 9.2); p=.005	.08
Wanted vs. Unwanted Pregnancy	13.7 (6.6, 20.7); p<.001	.26
Breastfed (3 levels, p-value only) [H]	.004	.38

VARIABLE	Coefficient [B] (95% CIs) and p-value for variable alone, unadjusted	p-value for Variable in Model [C]
Prior Pregnancy Complications	-4.0 (-9.4, 1.4); p=0.15	**.05**
Prior Pregnancy Birth Defects	-0.3 (-10.6, 10.0); p=.96	.85
Complications During Current Pregnancy	-3.3 (-8.5, 2.0); p=.22	.42
Compliance (missed AED doses) (3 levels, p-value only) [H]	.30	.64

[A] Only the 187 children with cognitive assessment at age 2 with the Bayley Scales of Infant Development were included in this analysis. Although there was only a trend for AED group in this initial analysis, the effects of epilepsy types were due to higher child IQs in the small Generalized Tonic Clonic Seizure (GTCS) group (n=13) with mean (CIs) = 108 (96:120) compared to partial seizure = 92 (88:95) and generalized seizures = 92 (88: 97). Re-analysis of data deleting GTCS group revealed no significant effects of epilepsy types, but significant effects of maternal IQ (F = 12.95, 1 df, p=.0004), age (F=4.3, 1 df, p=.04), dose (F=6.1, 1 df, p=0.01), folate (F=4.0, 1 df, p=.05) and AED x dose interaction (F = 3.0, 3 df, p=.03). Only valproate dose correlated with IQ (r=-0.59, p=.0009 without GTCS; r=-0.58, p=.0009 with GTCS). Age 2 and 3 IQs were highly correlated (r=.70; p<.0001) in children who completed both (n=161); [B] Estimated

regression coefficient (non-ordered categorical variables have only p value), 95% CI = 95% Confidence Intervals; [C] Model was the same as the primary analysis and included AED, maternal IQ, maternal age, standardized AED dose, gestational age, and preconception folate; [D] Variable included in primary model; [E] Standardized dose for pregnancy average (see Methods); [F] Three epilepsy types: localization related, idiopathic generalized, & generalized tonic clonic unknown if partial or generalized; [G] Unknown if idiopathic generalized or secondary generalized localization related; [H] Three categories (yes, no, not reported); [I] Education $\leq$ or > high school; [J] Four categories: Caucasian, Black, Hispanic, other; [K] Hollingshead Index.[10]

Web Figure Legends.

Web Figure 1. Means and 95% confidence intervals (horizontal lines) for child IQ as a function of subgroup defined by VPA group membership (VPA vs. Non VPA, i.e., other 3 AEDs) and propensity score subgroup[18] (above-median vs. below-median). The below-median group was further subclassified by epilepsy type (see Statistical Analysis).

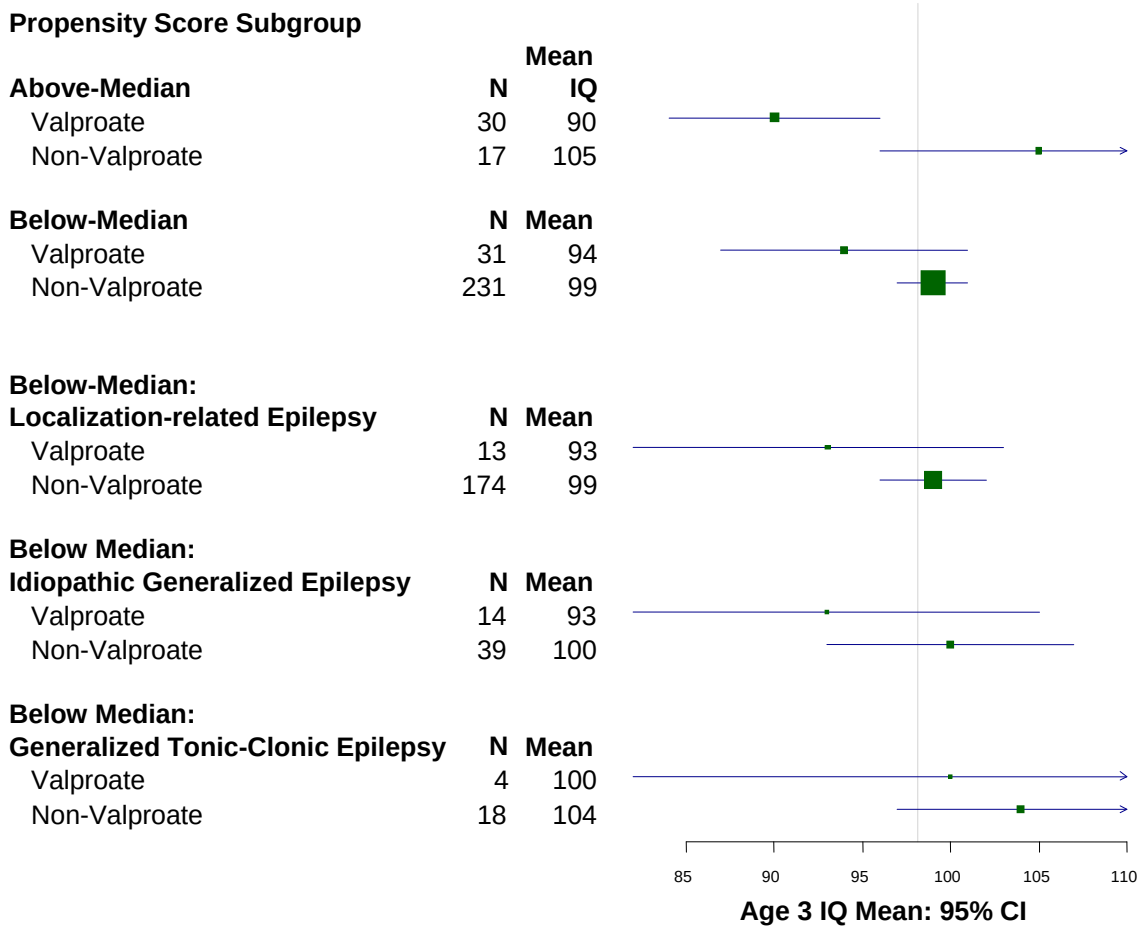
Web Figure 2. Means and 95% confidence intervals (horizontal lines) for child IQs as a function of maternal age and AED group. Low maternal age is below median for all mothers (30.7 years), and high maternal age is above median. Child IQs are adjusted for factors in the primary model except maternal age. In this and subsequent figures, the vertical line is the mean IQ across all children, the middle of the boxes on the horizontal lines are means for the subgroups, and the box size depicts sample size.

Web Figure 3. Means and 95% confidence intervals (horizontal lines) for child IQ as a function of USA vs. UK site and AED group. Child IQs are adjusted for factors in the primary model.

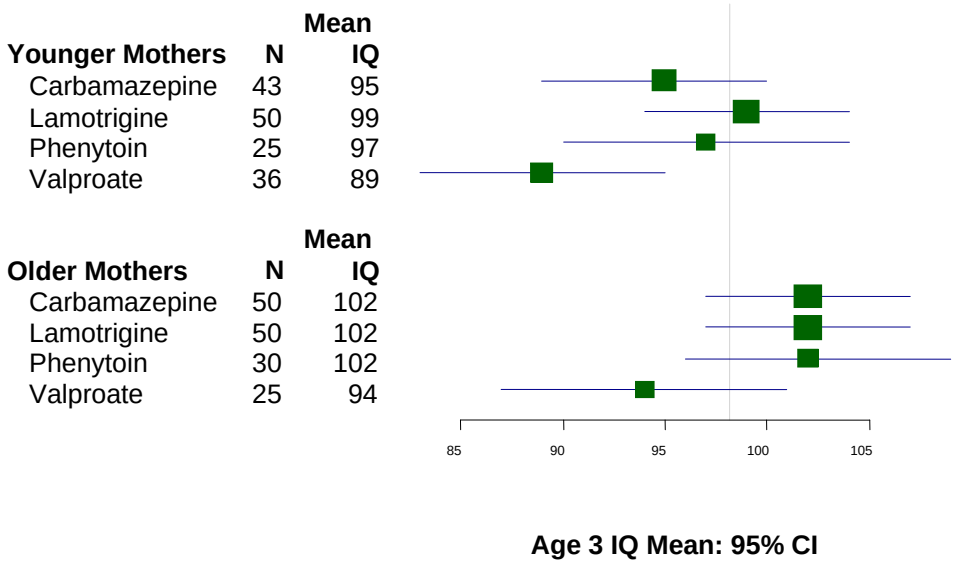
Web Figure 4. Means and 95% confidence intervals (horizontal lines) for child IQ as a function of breastfeeding and AED group. Child IQs are adjusted for factors in the primary model.

Web Figure 5. Relationships of child IQ - mother IQ differences vs. dose (pregnancy average) for the four AEDs. Correlations (r values) and p values given for each AED group. Only valproate exhibited a significant dose effect. Based on the intent-to-treat sample (n=309). Seventy-seven child IQ values were imputed (see Statistical Analysis).

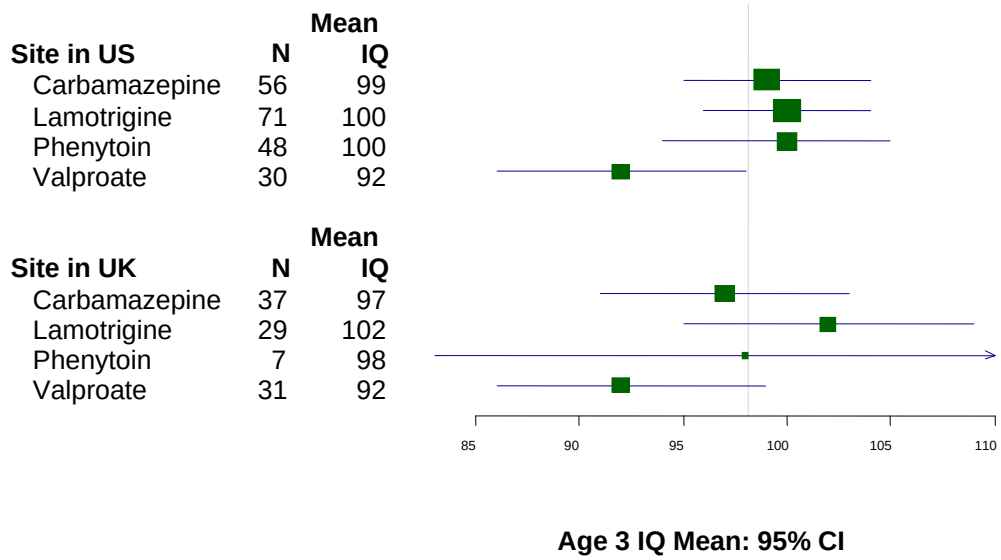
Web Figure 1.


Propensity Score Subgroup
Mean
Above-Median N IQ
Valproate 30 90
Non-Valproate 17 105
Below-Median N Mean
Valproate 31 94
Non-Valproate 231 99
Below-Median:
Localization-related Epilepsy N Mean
Valproate 13 93
Non-Valproate 174 99
Below Median:
Idiopathic Generalized Epilepsy N Mean
Valproate 14 93
Non-Valproate 39 100
Below Median:
Generalized Tonic-Clonic Epilepsy N Mean
Valproate 4 100
Non-Valproate 18 104
85
90
95
100
105
110
Age 3 IQ Mean: 95% CI

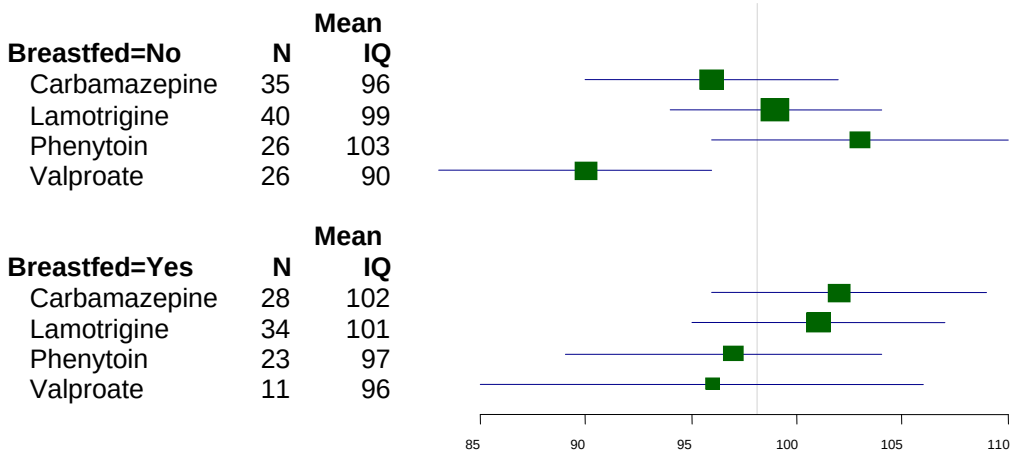
Web Figure 2.


Younger Mothers N Mean IQ
Carbamazepine 43 95
Lamotrigine 50 99
Phenytoin 25 97
Valproate 36 89
Older Mothers N Mean IQ
Carbamazepine 50 102
Lamotrigine 50 102
Phenytoin 30 102
Valproate 25 94
85
90
95
100
105
Age 3 IQ Mean: 95% CI

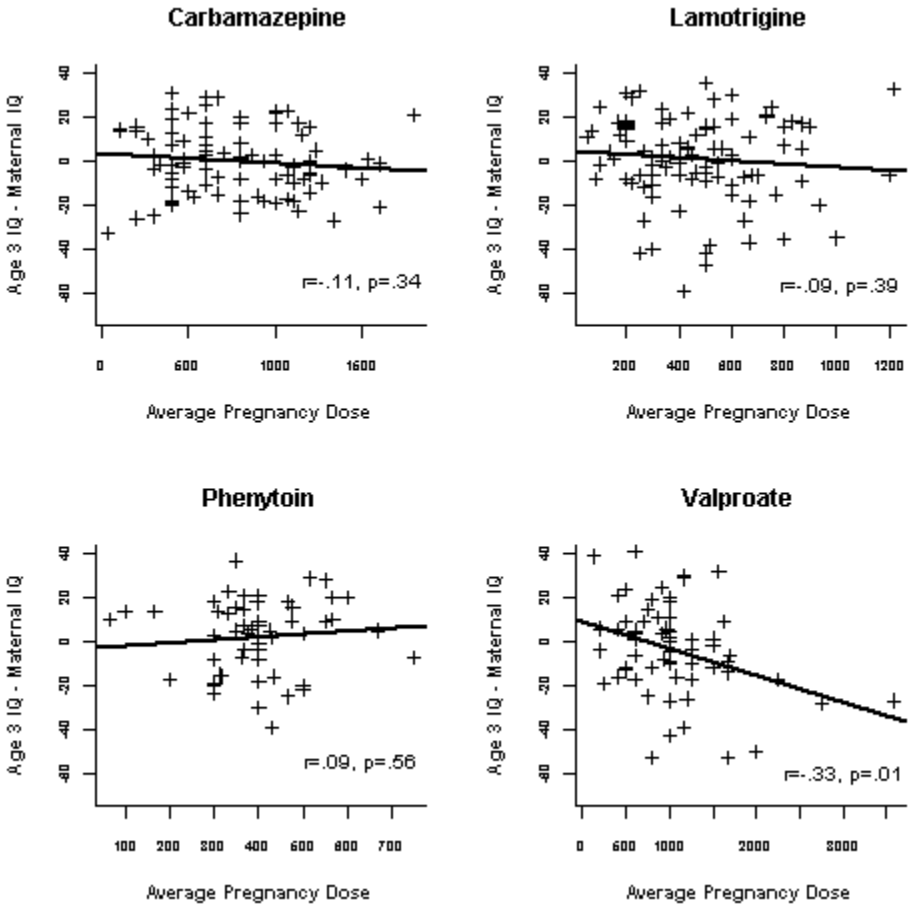
Web Figure 3.


Site in US
N
Mean IQ
Carbamazepine 56 99
Lamotrigine 71 100
Phenytoin 48 100
Valproate 30 92
Site in UK
N
Mean IQ
Carbamazepine 37 97
Lamotrigine 29 102
Phenytoin 7 98
Valproate 31 92
85
90
95
100
105
110
Age 3 IQ Mean: 95% CI

Web Figure 4.


Mean
Breastfed=No N IQ
Carbamazepine 35 96
Lamotrigine 40 99
Phenytoin 26 103
Valproate 26 90
Mean
Breastfed=Yes N IQ
Carbamazepine 28 102
Lamotrigine 34 101
Phenytoin 23 97
Valproate 11 96
85
90
95
100
105
110
Age 3 IQ Mean: 95% CI

Web Figure 5.


Carbamazepine
Age 3 IQ - Maternal IQ
r=-.11, p=.34
Average Pregnancy Dose
Lamotrigine
Age 3 IQ - Maternal IQ
r=-.09, p=.39
Average Pregnancy Dose
Phenytoin
Age 3 IQ - Maternal IQ
r=.09, p=.56
Average Pregnancy Dose
Valproate
Age 3 IQ - Maternal IQ
r=-.33, p=.01
Average Pregnancy Dose